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Cancer weaponises lipids

Ovarian cancer disables NK in ascites through lipid uptake, blocking this restores immune function

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Every year, over 200,000 people are diagnosed with ovarian cancer throughout the world[1], and among all subtypes, 70% of the fatalities caused by this deadly form of cancer will sadly come from High Grade Serous Ovarian Cancer (HGSOC). Its overwhelming presence in ovarian cancer fatalities shows it is a clear target for the future of medicine in humanities' fight against cancer. Ovarian cancer can metastasize into other organs in the body. This includes the peritoneum, where the metastasis causes buildup of abdominal fluid called ascites. Ascites are lipid-rich regions which enable tumours to grow. Natural Killer (NK) T cells are important for the elimination of cancer cells, as they are able to recognise and secrete granzymes and perforins, killing these cells. In the ascites, these NK cells are unable to carry out their antitumor actions, therefore enabling cancer growth.

The current method of immunosuppression of NK T cells is poorly understood. The paper in Science Immunology by Slattery and colleagues[2] attempts to find a pathway by which this immune cell dysfunction is caused, creating a possible therapy for this dysfunction, and clearing up a gap in knowledge as to how ascites cause dysfunction. For this paper they used samples from eight therapy naïve patients undergoing cytoreductive surgery or laparoscopy, hoping to use this knowledge to improve their condition. Returning immune function to NK cells is a key target for therapies against cancer, as they increase the body's ability to fight against cancer.

Importance of Ascites

Slattery and colleagues have shown the profound effect ascites have in causing dysfunction in NK cells. They cultured NK cells in standard RPMI medium and in ascites. NK cells exposed to ascites showed significantly reduced antitumor activity. Even after switching the cells from ascites to RPMI after 24 hours, the dysfunction persisted. This confirmed the pre-existing idea that ascites is important in immune cell dysfunction. Repeating the experiment with healthy peritoneal fluid indicated that malignant ascites specifically drives immunosuppression NK cells in HGSOC. Understanding the underlying mechanisms could significantly enhance disease management. As such, ascites represents a critical focus for improving both our understanding and treatment of HGSOC, so that is what the authors chose to focus on.

Lipids and Metabolism

Natural killer (NK) cells typically rely on glucose and amino acids to function, but in the hostile metabolic landscape of malignant ascites, the authors wanted to see if there were any changes. When NK cells were cultured in ascites derived from ovarian cancer patients, metabolomic analysis revealed that, while glucose metabolism remained largely intact, the standout feature was a striking accumulation of lipids. Malignant ascites were found to be particularly lipid-rich, a consequence of tumour-driven upregulation of fatty acid synthase (FASN), which fuels lipogenesis and supports cancer cell survival. Lipidomic profiling of NK cells exposed to ascites showed substantial increases in both polar and neutral lipids. However, RNA sequencing revealed no upregulation of key lipogenic enzymes such as FASN or acetyl-CoA carboxylase (ACACA), suggesting that this lipid accumulation was not due to de novo synthesis but rather active uptake. Indeed, lipid depletion in the ascites following NK cell culture supported this conclusion. These findings offer an important clue to how the ovarian cancer microenvironment impairs innate immunity. Since in healthy individuals, NK cells are generally reliant on glucose and amino acids, this change in lipid profile provides a clue to Lipid depletion in ascites following NK cell culture indicated active lipid uptake.

NK cells require a baseline level of neutral lipids (Figure 1a) to function; therefore, lipid uptake itself was not surprising, it was instead the unique lipid profile of the dysfunctional NK cells that was of interest. Slattery and colleagues speculated there was dysregulation of lipid homeostasis causing cell dysfunction. Flow

cytometry was carried out on NK cells in ascites cultures after 3 days, which identified these cells as having reduced lipid droplet levels compared to those in RPMI culture. Analysis of ATP showed the cells were still reliant on glucose. This confirmed their doubts, the cells were indeed struggling to regulate lipids. This occurred due to a loss of the cell's capacity to buffer and store fat intracellularly, likely due to lipid overload and lipotoxicity[3].

This lipidome remodelling highlights a method of immunosuppression for future therapeutic intervention in ovarian cancer to focus on, ideally a method of returning lipid homeostasis.

Lipid and dysfunction

Since dysfunction was a result of increase lipid uptake, removing those lipids could help the cells return to function. The authors applied a lipid absorption and clarification agent, the intervention improved NK cell function and glucose uptake via increased expression of the Glut1 receptor. Additionally, lipid levels recovered to normal, enhancing antitumor activity such as IFN-γ production.

The recovery proves that NK cells have the capacity to return to their former function. Further trials using lipids from other sources ascites confirmed that lipids from ascites disrupted NK function, highlighting the need for beneficial environmental lipids. These findings suggest that completely blocking lipid uptake may be ineffective, as only specific lipids appear harmful. Prospective therapies which block lipid uptake completely could possibly be detrimental to the NK cells.

The next objective was to identify these specific lipids. Among the lipids which had increased uptake, several induced dysfunctions. Including the sphingolipid ceramide (Cer) and phospholipids phosphatidylserine (PS) and phosphatidylcholine (PC). Of all the lipids identified, PC had the most significant impact on reducing lipid droplet levels in NK cells. It was hypothesised that it achieved this through disruption of the Lands cycle, which is responsible for membrane remodelling and order using the chemical reactions deacylation and reacylation. These are controlled by enzymes. By looking at the transcription of genes which regulated these enzymes, such as *PLA2G7* and *PLA2G15,* Slattery and colleagues deduced that there were changes in their transcription. A special dye revealed the disruption in the membrane order caused by PC, visualising the perturbation it caused in plasma membrane order.

PC alongside other lipids was responsible for the dysregulation of lipid homeostasis. This arose due to PC causing changes in a fundamental process important for the cell membrane to maintain order, causing the entire functionality of the cell to decrease (Fig 1b). Therefore, these lipids responsible would be crucial targets for both understanding the different pathways, but also for medical treatment of HGSOC.

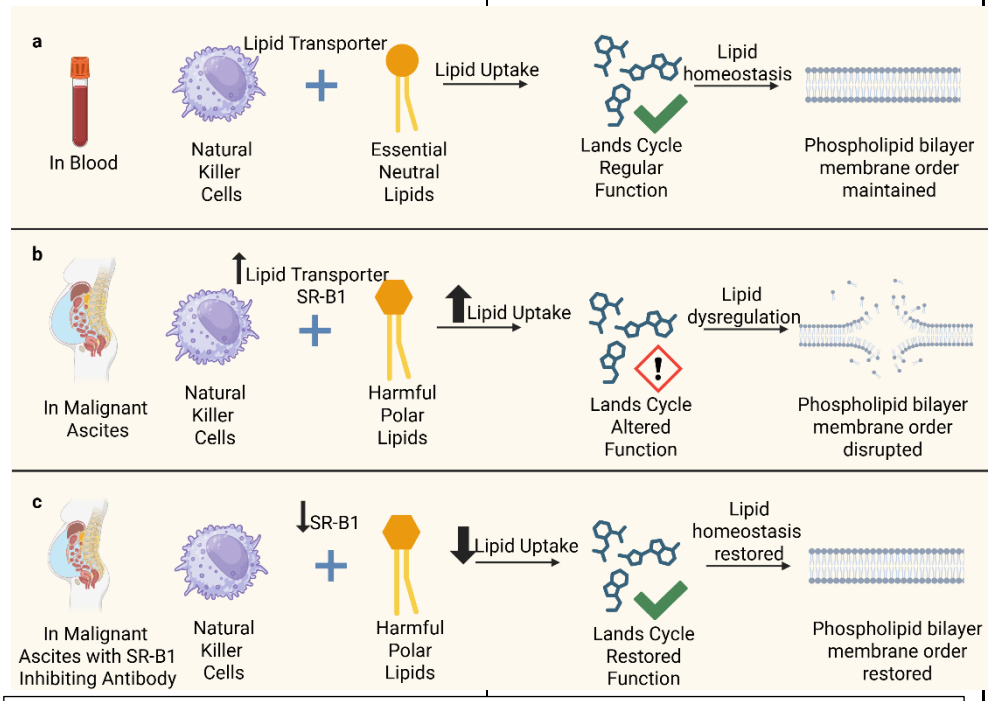


Figure 1: Detailing the different states of lipid regulation by Natural Killer cells in different environments. **a**, Highlights function in the blood or other organs, where homeostatic lipid intake enabled regular NK function. **b**, In malignant ascites, there is an uptake of PC by SR-B1 lipid transporter. These lipids disrupt the Land Cycle responsible for the upkeep of the phospholipid bilayer, causing disruption in the cell membrane and consequently cell function. **c**, In the presence SR-B1 antibody inhibitors we see a restored cell membrane in the NK cell, through restoration of the Lands cycle, aiding NK cell function recovery.

A cure?

A solution to this issue is to simply inhibit the uptake of PC. Many lipid transporters are upregulated in NK cells in ascites, and the one that is upregulated the most is the SCARB1 (SR-B1) lipid

transporter. Treating these NK cells with an SR-B1 blocking antibody showed improvements in NK cell function, and most importantly in its antitumor functions. This is likely due to SR-B1 being responsible for uptake of PC. Blocking this receptor prevented the lipids from malignant ascites from disrupting the cell membrane (Fig 1c.) and provides an early look into possible medicine which can be implemented to aid immune function in HGSOC patients.

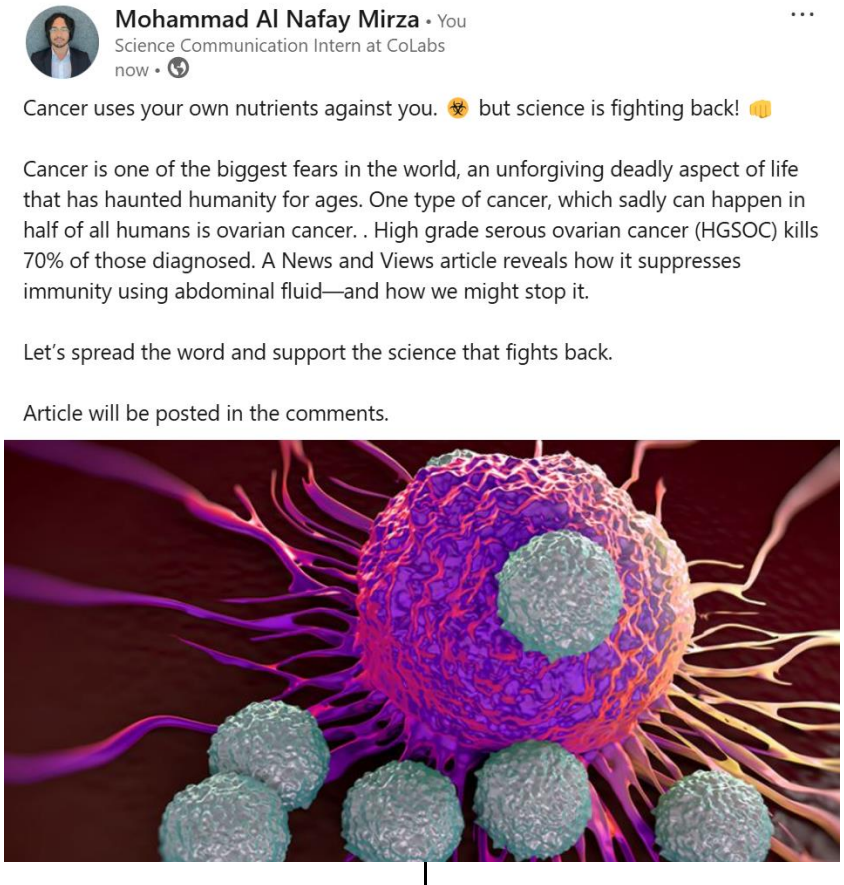
Conclusion

From the large number of deaths due to HGSOC, there is a need for effective therapeutic options to help patients suffering from it. Currently. 75% of patients die within 10 years of diagnosis[3]. This article has improved the scientific knowledge around one of the methods of HGOSC's survival. The paper emphasises ascites as a key tool of survival, with it having a complex micro-environment to enact its immunosuppression on a number of immune cells. It carried this out, using lipid remodelling through overload of polar lipids and lipotoxicity. Not only does it identify this method, it identifies the specific lipids involved in causing NK cell dysfunction. By identifying these molecules, early therapies can be created to inhibit their uptake, such as the SR-B1 inhibitor used by Slattery and colleagues in the paper. The paper also suggests that only targeting PC(36:1) uptake might not be ideal, and that a more holistic therapy targeting a multitude of the lipids in ascites that cause dysfunction may show even greater recovery in NK cell's antitumor responses.

This article provides the foundation for future research into malignant ascites' immuno-suppressive properties in NK. Future research can use more patients and different methods of testing to increase the quality and quantity of data. Scientists and medical professionals can leverage this research that prevent the changes in the NK lipidome that prevent or counteract ascites from causing dysfunction. This paper expands upon the current knowledge regarding HGSOC and provides a pathway which future therapies for cancer can take.

References

1. Lisio, M.A., Fu, L., Goyeneche, A., Gao, Z., and Telleria, C. *Int. J. Mol. Sci.* **20**, 952(2019)
2. Slattery, K. *et al. Sci. Immunol,* **10**, eadr4795(2025)
3. Shi, Y., Zhu, S., Shan, J., and Xu, Y., *Front. Oncol.* **15**, 1468196(2025)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now •
Cancer uses your own nutrients against you. but science is fighting back!
Cancer is one of the biggest fears in the world, an unforgiving deadly aspect of life that has haunted humanity for ages. One type of cancer, which sadly can happen in half of all humans is ovarian cancer. . High grade serous ovarian cancer (HGSOC) kills 70% of those diagnosed. A News and Views article reveals how it suppresses immunity using abdominal fluid—and how we might stop it.
Let's spread the word and support the science that fights back.
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